REMARKS

Claims

Claims 1-3, 8-13 and 22 are currently under examination pursuant to the restriction requirement mailed February 22, 2008.

Claims 17-18 are withdrawn from consideration as per the aforementioned restriction/election requirement.

Claims 4-7, 14–16, 19 and 20 were previously cancelled. Claims 8 and 21 are hereby cancelled without prejudice or disclaimer.

Claim amendments

The foregoing amendments comply with the provisions set forth under §1.116(b)(2). To this end, claim 1 has been amended to delete the claimed variants of the antibody molecules. Claim 1 further incorporates the subject matter of claim 8, which is hereby cancelled.

Amended claim 9 recites methods for producing crystals of the claimed antibody molecules. Claim 21 is hereby cancelled. Applicants' amendment of the claims should not be construed as acquiescence to any ground of rejection.

It is respectfully submitted that the amendments do not recite new matter. Entry thereof is respectfully requested.

Biological deposits

Applicants submit that the claimed antibodies can be publically obtained. To this end, paragraph [0037] of Applicants' published specification (US publication No. 2007-0122411) expressly teaches that "Mab C225 (cetuximab) is a *clinically proven* antibody which binds to the EGF receptor [and that] Mab C225 (cetuximab) is a chimeric antibody whose variable regions are of murine origin and whose constant regions are of human origin. It was described for the first time by Naramura et al., *Cancer Immunol. Immunotherapy* 1993, 37: 343-349 and in WO 96/40210 (i.e., International Application No. PCT/US96/09847)." Applicants further note that US serial No. 08/973065, which is a continuation-in-part of the US national phase of PCT/US96/09847 (US 08/482,982), has matured into US patent No. 7,060,808 (ImClone Systems, Inc.). The disclosure in the '808 patent provides guidance regarding the structure of the C225 antibody (and ATCC accession numbers of the DNA

sequences encoding the C225 anitbody). See the disclosure in the Figures 15–16 of the '808 patent. Since this deposit met the US requirements as a US patent is now issued, Applicants respectfully submit that the requirements under 37 CFR §1.803 are duly satisfied. In any case, this issue is moot issue since antibody molecules making up the claimed crystals are commercially available (e.g., Erbitux®). See attached information published by the Food and Drug Administration (FDA).

As for the expressed requirement that Applicants provide a biological deposit, the Examiner's contentions are respectfully traversed. As expressly stated in §2404.02:

> A deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation. No deposit is required, however, where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. Tabuchi v. Nubel, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); Ex Parte Hata, 6 USPQ2d 1652 (Bd. Pat. App. & Int. 1987) (Emphasis added)

Inasmuch as the claimed antibodies can be publically obtained, and the specification provides explicit guidance on methods for obtaining crystals therefrom, the PTO's contentions are without merit. Favorable reconsideration is earnestly solicited.

Rejections under 35 U.S.C. §112, ¶1

Claims 1–3, 8–13 and 22 are rejected under this section as allegedly lacking sufficient written description and/or enablement. The written description and enablement rejections under this section are directed to antibody variants and derivatives (such as PEGylated antibodies) of mAb c225, which are presently not claimed. It is submitted that the foregoing amendments render the rejection moot.

With respect to the method(s) for obtaining the claimed crystals, the Examiner alleges that crystallization of proteins is complex and the instant specification does not provide an enabling disclosure on crystallization of antibodies other than Erbitux ®. In the paragraphs spanning pages 8-10 of the Office Action, the Examiner further asserts that protein crystallization is complex and that absent recitation of the exact conditions stated under Examples 2 and/or 3 of the present specification, the instant claims are non-enabled. This contention is respectfully traversed.

Contrary to the Examiner's contention, Applicants submit that the present disclosure provides explicit guidance on how to make and use the crystals of the present invention.

Reagents and conditions that are applicable to the claimed methodology of crystallization of the claimed molecules are described in detail. To this end, Example 2 provides a disclosure of crystallization of Erbitux with ammonium sulfate. Example 3 relates to another embodiment, wherein crystallization of Erbitux with ethanol is provided. See, pages 46–47 of the specification. Methods for visually and/or spectroscopically characterizing the crystals of the present invention (for example, with respect to size and or IR spectra) are also provided. See, Examples 6–7 at page 49 of the specification.

It is now well-settled that the USPTO must have adequate support (evidence or reasoning) for its challenge to the credibility of Applicants' statements of enablement. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

Furthermore, as stated in *Marzocchi*, at 370, Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. § 112, ¶1. The Examiner cites Weber et al. (*Methods in Enzymology*, 1997), MacPherson et al. (*Journal of Biochemistry*, 1990) and Drenth et al. (*Principles of X-ray crystallography*, 1st edition: 1990) to support the contention that protein crystallization is unpredictable. The USPTO's reliance on these references is respectfully traversed. MacPherson is fully thirteen years before the earliest priority date of the instant application, and as such, fails to appreciate the progress made in the field of X-ray crystallography during this period. MacPherson further provides an overview of challenges associated with crystallization of large macromolecules, including, viruses, polynucleotides, and the like. Although not much specific guidance as to crystallization of antibody molecules, in Fig. 6, the reference teaches that crystals of albumin can be obtained. Drenth generically teaches that it is difficult to predict conditions for growing protein crystals, but fails to provide any specific guidance on the crystallization of globular (i.e., water-soluble) proteins, such as antibody molecules. It is art appreciated, for example, that transmembrane (i.e., integral) proteins are more difficult to crystallize than globular proteins (due to, for example, difficulties in expression, difficulties in solubilization,

and difficulties in crystallization). Gloubular and cytosolic proteins face fewer challenges. Anti-tumor antibody molecules, and particularly the Fab portions that bind to antigens of interest, have been crystallized at high resolutions (see, Harris et al. "The three-dimensional structure of an intact monoclonal antibody for canine lymphoma" *Nature*, 360(6402):369-72, 1992). Favorable reconsideration is respectfully requested. Although Weber notes that antibody crystallization has challenges, the references' disclosure of antibody crystals outweigh the USPTO's broad allegations regarding non-enablement.

Accordingly, Applicants respectfully submit that the rejection fails to present sufficient evidence to doubt the objective enablement provided in Applicants' specification that claimed molecules can be prepared in a manner recited in the claims. Thus the rejection should be withdrawn.

Contrary to the PTO's contentions, Applicants further submit that a skilled biochemist who is equipped with the claimed antibody molecules and who is presented with the disclosure in the present specification could routinely produce the claimed antibody crystals without undue experimentation. The sequences of the claimed antibody molecules, for example, chimeric monoclonal antibody c225, were well-appreciated in the art prior to the filing date of the present application (thereby allowing recombinant expression and purification of large batches of the protein). Techniques for generating crystals of such antibody molecules, and use thereof, for example, in developing formulations, medicaments, and the like are described in detail by Applicants' own specification. See, for example, the disclosure bridging pages 14–18 of the present specification. As such, Applicants' specification provides a fully enabling disclosure of the methods for making and using the crystals of the present invention.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention without undue effort. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

Reg. No. L0510
For Applicant(s)

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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